REMARKS

Claims 29-46 are currently pending in the present application with claims 29 and 42 being in independent form. Claims 29 and 42 are currently amended, and claims 43-46 are newly added. Support for the amendments to claim 29 can be found, for example, in paragraph [0001], page 4, as well as pages 10-11 of the specification as filed. Support for newly added claims 43-46 can be found, for example, on page 10, lines 14-27; page 2, lines 26-30, and page 2, line 24).

Claims 29, 30 and 42 have been rejected under 35 U.S.C. §103(a) as being obvious over Zhou et al. (Exp Biol Med (Maywood). 2002 Mar; 227(3):214:22) (hereinafter "Zhou") in view of United States Patent Publication No. 2002/0090670 to Mallee (hereinafter "Mallee"). Applicants' respectfully traverse.

Claim 29 is directed toward a method for restoring thiol homeostasis in a subject in need thereof, comprising administering to said subject an effective amount of a mixture of peptides comprising at least 6.5 %wt cysteine, wherein at least 80% of the cysteine residues are in the oxidized form.

The recently revised Examiner guidelines for assessing obviousness set forth detailed requirements based on asserted rationales for obviousness. The Rationales To Support Rejections Under 35 U.S.C. §103 provide the following possible rationales:

> (A) Combining prior art elements according to known methods to yield predictable results;
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> (B) Simple substitution of one known element for another to obtain predictable results;
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> (C) Use of known technique to improve similar devices (methods or products) in the same way;
>
> (D) Applying a known technique to a known device (method or product) ready for improvement to yield predictable results;
>
> (E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;

> (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; and
>
> (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

See MPEP 8th Edition, rev. 6, §2141. Applicants proceed with the understanding that this rejection conforms to rationale G quoted above. The MPEP further sets forth the requirements for an obviousness rejection under this rationale:

> To reject a claim based on [rationale G], Office personnel must resolve the Graham factual inquiries. Then, Office personnel must articulate the following:
>
> (1) a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings;
>
> (2) a finding that there was reasonable expectation of success; and
>
> (3) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.
>
> The rationale to support a conclusion that the claim would have been obvious is that "a person of ordinary skill in the art would have been motivated to combine the prior art to achieve the claimed invention and that there would have been a reasonable expectation of success." DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co., 464 F.3d 1356, 1360, 80 USPQ2d 1641, 1645 (Fed. Cir. 2006). **If any of these findings cannot be made, then this rationale cannot be used to support**

a conclusion that the claim would have been obvious to one of ordinary skill in the art. [emphasis added]

See MPEP 8th Edition, rev 6, §2143

As part of a *prima facie* case of obviousness, an examiner must establish some reason to combine or modify the references. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1731 (2007); *Takeda Chemical Industries, Ltd. v. Alpharpharm Pty., Ltd.*, 492 F.3d 1350, 1356-1357 (Fed. Cir. 2007). The *KSR Int'l* Court acknowledged the importance of identifying a reason that would have prompted a person of ordinary skill in the art to combine or modify the elements in the way the claimed invention does. *KSR Int'l*, 127 S.Ct. at 1731; *Takeda Chemical*, 492 F.3d at 1356-1357. Repeatedly throughout the *KSR Int'l* decision, the Court discussed the importance that the result obtained by a particular combination or modification was predictable to one of ordinary skill in the art. *KSR Int'l*, 127 S.Ct. at 1731 and 1739-1742.

A combination of known elements will not yield predictable results if the references teach away from the claimed invention. *Takeda Chemical*, 492 F.3d at 1359; *Ortho-McNeil Pharmaceutical, Inc. v. Mylan*, 520 F.3d 1358, 1364 (Fed. Cir. 2008); and *Ex parte Ikeda*, App. No. 08/352,079, Appeal 2008-0492, Slip Op. at 7 (BPAI Mar. 26, 2008). For example, in *Takeda Chemical*, the post-*KSR* Federal Circuit noted that the recited compound, which was a modified version of compound b, was not recognized at the pertinent time as a suitable candidate for treatment of Type II diabetes. 492 F.3d at 1359. *Takeda Chemical* involved United States Patent No. 4,687,777, which was directed to a compound for the treatment of Type II diabetes. *Id.* at 1352-1354. The defendant argued that the patent was obvious in view of a reference that disclosed compound b, because the claimed compound could be synthesized from compound b by routine means. *Id.* at 1357. However, the Federal Circuit affirmed that the patent was not obvious because the prior art taught away from choosing compound b as a starting point. *Id.* at 1359-1361. Compound b was known to have unwanted side effects, and there was nothing in the prior art to suggest that homologation would decrease the unwanted side effects. *Id.* at 1359-1360.

In a more recent case, the Board reversed an examiner's rejection for failing to provide the requisite reason to combine the references. *Ikeda*, App No. 08/352,079 at 7. The *Ikeda* application was directed to a method of removing hydrocarbons from exhaust gases.

Id. at 2. In pertinent part, the claims recited an absorption catalyst B located downstream of a catalyst A in the direction of the exhaust gas. The claims were rejected as unpatentable under 35 U.S.C. § 103 in view of Swaroop, Abe and Patil. *Id.* at 3. Swaroop taught positioning the absorption catalyst B upstream of catalyst A. *Id.* at 5. To remedy the deficiency in the art, the examiner cited "Patil and Abe as evidence of the 'conventionality of positioning the adsorbent catalyst 1 either upstream or downstream of a [three-way] catalyst 3' and thus conclude[d] that it would have been obvious to one of ordinary skill in this art to select an appropriate location for the adsorbent catalyst 16 in the apparatus of Swaroop ...." *Id.* at 5-6. The Board held that:

> The Examiner has failed to provide any cogent reason or technical discussion to support the conclusion that one of ordinary skill in this art would have employed the relative positions of the catalysts in Abe and Patil without the use of the other teachings of these references, namely an auxiliary heater and bypass lines with valving. Second, the Examiner has not explained why one of ordinary skill in this art would have used the teachings of Patil, requiring bypass lines and valving, when Swaroop specifically ***teaches away*** from the use of valving and bypass lines [*citation omitted*]. Third, the Examiner has not supplied convincing reasoning or technical discussion to support the proposed switch in relative position of the catalysts when Swaroop specifically teaches that the exhaust gas is "modified" by the adsorbent catalyst and this modified form of the exhaust gas is *then* sent to the main or three-way catalyst to undergo conversion to innocuous products [*citation omitted*]. ... Fourth, the Examiner has not explained why one of ordinary skill in this art would have ***proceeded contrary to the teachings of Patil***, namely the teachings that "it is not possible merely to place zeolite 'in-line' in the exhaust system with the [main] catalyst has reached an effective temperature and unconverted hydrocarbons would still be discharged to the atmosphere" [*citation omitted*].

Emphasis added, *Ikeda*, App. No. 08/352,079 at 7.

Following the reasoning stated in *Takeda Chemical* and *Ikeda*, the Office Action must provide some explanation why one of ordinary skill in the art would modify the teachings of Zhou (i.e., restoring GSH to inhibit ethanol-induced liver injury) by administering the preparation of Mallee.

Zhou describes the effect of metallothionein (MT) in treating alcohol liver injury by studying MT -transgenic mice, i.e., mice that overproduce MT. Zhou did not investigate orally administering MT. Zhou suggests that increasing antioxidant defense is a potential therapy for alcoholic liver disease (Office Action, page 4).

It should be noted that Zhou also concludes that supplementation with antioxidants as protection against alcohol liver injury has been widely investigated, but that no antioxidant has been advised for clinical treatment. (Zhou, page 221). Hence, there is no general motivation to use antioxidants for such treatment. On the contrary, the art as such teaches away from using common antioxidants in treating alcohol-induced injury.

Zhou then continues by concluding, based on their studies, that MT, i.e. not antioxidants in general, may be useful in such treatment. MT (metallothionein) is a group of proteins which is very high in cysteine: about a third (33%) of their amino acids (Zhou, page 215). MT contains some 50-70 amino acids, and thus has a molar weight in the range of 6,000-8,000. The cysteine residues in MT will be in their reduced form, since it is produced in the mouse body and Zhou stresses the antioxidant (= reducing) activity of MT.

The results obtained by Zhou provide no indication that replacing MT-transgenic with *other* proteinaceous material, which is (orally) *administered*, and which has a much lower cysteine content, wherein the cysteines are in the oxidized form, as required by the claimed invention would be effective in a similar treatment.

The peptides to be used in the instant invention - as distinct from the protein of Zhou, are administered, i.e., exposed to the (food) processing and digestive conditions, and not produced by the body itself. They are a mixture of peptides derived from common proteins, especially whey proteins, and are significantly shorter (300-6,000, especially 400-5,000 kDa) than MT. They have a lower cysteine contant (6.5-20%, typically around 7-7.5 %, as compared to some 33% for the MT), and most importantly, are in the oxidized form. This means that the thiol groups of the cysteine residue (-SH), have been oxidized to produce disulfide links (-S-S-)

between couples of cysteine residues, and the peptides have lost most of their (direct) reducing power. In view of the teaching of Zhou, no effect from such oxidized, i.e., not reducing, not directly anti-oxidative peptides could be expected. Examples 8 and 10 provide evidence that the claimed invention has the desired effect.

According to the Office Action, Mallee teaches a preparation comprising cysteine-rich peptides, comprising 7-20 w/w% cysteine. However, Mallee does not provide any motivation to one of ordinary skill in the art to modify the teachings of Zhou (i.e., MT-transgenic) to incorporate the preparation of Mallee to teach the claimed method. Specifically, neither Mallee nor Zhou, either alone or in combination, teach or suggest the claimed method for restoring thiol homeostasis in a subject in need thereof, comprising administering to said subject an effective amount of a mixture of peptides comprising at least 6.5 % wt cysteine, wherein at least 80% of the cysteine residues are in the oxidized form.

Claims 30-46 depend from and further limit claim 29 and are believed to be non-obvious for at least the aforementioned reasons.

CONCLUSION

In view of the amendments to the claims and the remarks, Applicants respectfully request reconsideration and withdrawal of the rejections asserted against the pending claims, and allowance of claims 29-46.

Respectfully submitted,

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